

## Comment

Studies of other areas of southeast Asia are needed to validate the epidemiological utility of the marker for mapping resistance. More information is also needed about the relationship between more proximal kelch13 mutations (before aminoacid position 440) and resistance to define cutoffs. All this information should be available soon.

If the kelch13 propeller mutations are validated as epidemiological markers, then researchers need to consider how such markers should be used. Although it will probably be necessary to amplify and then sequence all or most of the gene to identify mutations (there are too many mutations for single nucleotide polymorphism PCRs), this is still much easier than phenotyping. Filter paper blood spots or rapid diagnostic tests will provide enough DNA and can be readily collected and easily stored pending transport to a reference laboratory. The first priority is to define how far artemisinin resistance has spread in east Asia. Screening elsewhere should start and thresholds for action established (indeed, exactly what form such action should take must also be decided urgently). Mutations in the kelch13 propeller region occur at low frequencies in natural populations, and it needs to be established whether or not these mutations are associated with slow parasite clearance with artemisinin treatments. It might well be that several other genetic changes are needed to confer the stable resistant phenotype on *P. falciparum*,<sup>12</sup> although the successful laboratory selection experiment<sup>9</sup> is not reassuring. The discovery of a molecular marker of artemisinin resistance is an important breakthrough. Let us hope

we can now use it to help contain this threat before it spreads to infect the rest of the malaria-endemic world.

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I declare that I have no competing interests.

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## Russia: lessons for alcohol epidemiology and alcohol policy

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In *The Lancet*, David Zaridze and colleagues<sup>1</sup> present additional important information about alcohol epidemiology: a large prospective observational study of 151 000 adults in three Russian cities, followed up for mortality for up to 11 years. The results corroborate findings of previous studies, including a large retrospective case-control study<sup>2</sup> from the same team, indicating that mortality in Russia, especially for men, is very strongly affected by alcohol consumption. For example, risks of death at age 35–54 years were 16% (15–17), 20% (18–22), and 35% (31–39) for male

smokers who reported consuming less than 1, 1–2.9, or 3 or more bottles of vodka per week, respectively.

In fact, the time series of alcohol consumption per head and of all-cause mortality for men have been almost parallel for most of the past 60 years.<sup>3–5</sup> What, then, is specific about the Russian experience, and how does Russia contribute to our understanding of the alcohol-attributable burden of disease?

The adverse effect of heavy drinking, and particularly of heavy episodic drinking,<sup>6,7</sup> is clearly shown by Russian research studies.<sup>1–4</sup> The exponential nature of the

relation between average alcohol consumption and mortality<sup>8</sup> is well portrayed in large Russian population samples such as Zaridze and colleagues' study,<sup>1</sup> in which substantial numbers of people report drinking three or more half-litre bottles of vodka per week. Yet the exponential curves for dose-response relations between average volume of alcohol consumption and the mortality risk of various diseases,<sup>9</sup> which are usually derived from meta-analyses of all epidemiological studies, cannot fully explain the attributable fractions noted in studies based on large population samples from Russia.

Consequently, when modelling Russia and surrounding countries with similar drinking patterns, the usual methods<sup>9,10</sup> for estimating burden of alcohol-attributable disease in the comparative risk assessment of the last Global Burden of Disease study had to be abandoned, and region-specific relative risks from the earlier Russian case-control study of Zaridze and colleagues<sup>2</sup> used instead (for estimation of global and regional burden of disease attributable to various risk factors in 2010 see Lim and colleagues' work;<sup>11</sup> and the Institute for Health Metrics and Evaluation website).

On its own, the overall volume of alcohol consumed in Russia, albeit high, cannot explain the high alcohol-attributable mortality; it is the combination of high overall volume with the specific pattern of episodic binges that is necessary to explain the high level and fluctuating trends of total and alcohol-attributed mortality in Russia. The study by Zaridze and colleagues<sup>1</sup> depicts this theory: even in the highest-drinking group of men, with an average reported consumption of about five half-litre bottles of vodka per week, almost 3 days per week with abstinence were reported. Since the prevalence of smoking in men was so high, varying from 68.9% in the lowest alcohol intake group to 89.4% in the highest alcohol intake group, Zaridze and colleagues limited their main analyses to the effects of drinking among smokers. So perhaps, particularly at older ages, some of the alcohol effect reported could be attributable to an interaction between the effects of smoking and of alcohol consumption.

Attributing the effect of alcohol to episodic heavy drinking patterns does not mean that alcohol policy directed at the population level to reduce overall



availability does not work in Russia.<sup>12</sup> On the contrary, as analysis of the experiment of Mikhail Gorbachev's 1984 alcohol restrictions indicated, reduction of alcohol availability rapidly led to less episodic heavy drinking and to greatly decreased mortality, especially for alcohol-attributable causes of death in men.<sup>3,4</sup> A more recent example is provided by the Russian alcohol policy reforms of the first decade of the 21st century, where a decrease since 2006 in the availability of alcohol was again associated with substantially decreased alcohol consumption and mortality.<sup>5</sup> In other words, the fact that alcohol consumption has such a huge effect on mortality opens a door for interventions to decrease the high mortality rate in Russia, especially for men—by implementing alcohol policy that reduces the availability of alcohol, such as via price increases. Since the average life expectancy from birth for men in Russia is still only 64 years, ranking among the lowest 50 countries in the world, more effective alcohol and tobacco policy measures are urgently needed.

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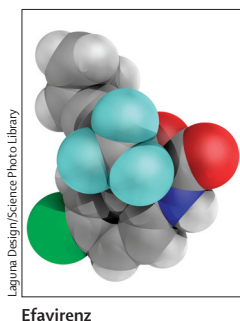
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For the Institute for Health Metrics and Evaluation website see <http://www.healthmetricsandevaluation.org/gbd/research/project/global-burden-diseases-injuries-and-risk-factors-study-2010>

For more on Russia's population data see <https://www.cia.gov/library/publications/the-world-factbook/>

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## Antiretroviral dose reduction: good for patients and rollout



Of the 35 million people living with HIV, almost a third are already on antiretroviral therapy, and the current aim is to increase substantially the number of people on medication during the next 5–10 years.<sup>1</sup> WHO recommends a regimen of the non-nucleoside reverse transcriptase inhibitor efavirenz, and the nucleotide and nucleoside reverse transcriptase inhibitors tenofovir and lamivudine (or emtricitabine), as the preferred primary fixed-drug combination treatment.<sup>2</sup> This recommendation is based on extensive evidence supporting efficacy, simplicity, and tolerability, and allows for one drug procurement schema that is affordable, can be safely used in pregnancy, can be combined with tuberculosis drugs, and is effective against hepatitis B virus.

In *The Lancet*, Rebekah Puls and colleagues present results from the ENCORE1 trial,<sup>3</sup> focusing on the dose of the efavirenz component of this regimen. Although efavirenz is generally well tolerated in patients on stable treatment, the drug often causes CNS-related symptoms in the first few days. These effects usually subside on continued use because excretion is accelerated by induction of cytochrome P450 enzymes in liver.<sup>2</sup> Since first being marketed in 1998, efavirenz has been dosed at 600 mg once a day. However, the unpublished dose-finding phase 2 trial that led to choice of the 600 mg dose in phase 3 trials, and that compared 200 mg, 400 mg, and 600 mg doses (45 patients per group), found that virological effects were similar between groups.<sup>4</sup>

The ENCORE1 investigators randomly assigned more than 600 people who were starting treatment for the first time to either 400 mg or 600 mg of

efavirenz a day, as part of a standard triple therapy regimen. The researchers found high, similar, and statistically non-inferior proportions of patients with viral load suppression at 48 weeks with the lower dose (302 of 321 [94.1%] in the 400 mg group and 285 of 309 [92.2%] in the 600 mg group had HIV-RNA <200 copies per mL plasma [difference 1.85%, 95% CI –2.1 to 5.79]). This endpoint is a well accepted and validated surrogate endpoint for clinical efficacy in the field and by medical assessment authorities. Efavirenz plasma concentrations vary depending on host genetic variations in the P450 enzyme system and volume of distribution within the body. However, the non-inferior efficacy finding comparing 400 mg versus 600 mg was seen irrespective of ethnic origin and body-mass index. Another important finding was that the risk of efavirenz-specific adverse drug reactions was reduced from 47% in the 600 mg group to 37% in the 400 mg group (difference –10.5%, 95% CI –18.2 to –2.8;  $p=0.01$ ). Finally, recovery of CD4 lymphocytes was significantly more pronounced when dosed at 400 mg, with a mean benefit of 25 cells/mm<sup>3</sup> at 48 weeks (95% CI 6–44,  $p=0.01$ ). If not a chance finding, this result suggests that the 600 mg dose of efavirenz could be associated with some degree of host-cell toxicity that is seen less frequently when dosed at 400 mg. Therefore, all three key findings from ENCORE1 favour the lower efavirenz dose.

ENCORE1 provides important new information for planning the WHO-led global antiretroviral treatment rollout programme. To treat 10 million people with efavirenz for a year, we calculate that 2190 metric tonnes of the drug need to be produced

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